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# **Novel diagnostic approaches and cost–benefit balance of treatment of immune-mediated and rare disease in the era of biologic drugs: Lessons from the 15th Turin Congress on Immune Pathology and Orphan Disease**

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The 15th Congress on Immune Pathology and Orphan Disease held in Turin, Italy, on January, 20–22, 2012, was especially dedicated to the following issues:

- The intriguing connections between immune-mediated diseases, immunodeficiencies and lymphoproliferative disorders and the rationale for innovative treatments;
- Novel diagnostic approaches to immunologic and rare diseases;
- The expanding role of videocapillaroscopy in the diagnosis and clinical monitoring of systemic sclerosis-related disorders;
- Identification criteria of high risk patients with antiphospholipid syndrome;
- Algorithms of treatment of rheumatoid arthritis with TNF antagonists;
- Cost–benefit balance of RA treatment in the era of biologic drugs.

The traditional classification of diseases of the immune system that separates immunodeficiencies [1], allergy and hypersensitivity diseases, autoimmune diseases, and lymphoproliferative disorders is currently outdated. Many experimental observations and clinical data support the existence of a widespread overlapping. Baldovino et al. [2, present issue] reported on the most recent genetic and etiologic data linking common variable immunodeficiency (CVID) with some autoimmune diseases, and emphasized the need to systematically search for a CVID in patients with immune-mediated diseases showing deficiency in IgG, IgM or IgA levels. The authors also focused on the possible role of viral and bacterial infections as causative agents of autoimmune and inflammatory manifestations in CVID [3].

Many features link autoimmune disorders (AD) and lymphoproliferative disorders [4]. The risk of developing non-Hodgkin's lymphoma (NHL) in Sjögren's syndrome, rheumatoid arthritis and systemic lupus erythematosus has been found to be 4 to 40 folds greater than in the general population. B-cell activation and proliferation are part of AD and are essential factors for the onset of malignant cell clones in a deregulated immunological environment. Tarella's review [5, present issue] provides details on the main epidemiological features regarding NHL incidence in AD, the pathogenetic factors that favor lymphoma onset and some recent advances in therapeutic approaches that are effective in both autoimmune and malignant lymphoproliferative disorders. Indeed, targeting deregulated or malignant B-cells is the goal of some newly developed treatments. The prototype is the anti-CD20 monoclonal antibody, rituximab. It has substantially modified the prognosis of B-cell NHL [6] and is also an effective new therapeutic opportunity for some AD [7]. Similarly, intensified treatments with autologous hematopoietic stem cell transplant that were developed for high-risk lymphoma are now under advanced investigation for use in

some refractory AD. The successful use of rituximab and ASCT in both AD and NHL further emphasizes the close link between these two entities.

With regard to the novel diagnostic approaches to immunologic and rare diseases [8], lab-on-a-chip devices are analytic platforms that will open revolutionary opportunities in diagnostic testing [9]. They are completely automated devices which allow manipulation of small volumes of fluids and miniaturization of complex laboratory procedures onto small microchips. These analytical microsystems integrate various functional modules into a single device, sparing reagents and biologic samples, and delivering results in a fast turnaround time. In this special issue a variety of lab-on-a-chip devices developed for immunoassays and genomic testing that are especially dedicated to the diagnosis of rare diseases have been reviewed by Menegatti et al. [10, present issue] including those using multiplexed, miniaturized and ultra-sensitive technologies than can simultaneously identify multiple markers in the routine clinical setting of immuno-mediated diseases.

As far as the expanding role of nailfold videocapillaroscopy is concerned, this technique has already been widely accepted as the most valuable tool for the early diagnosis of disorders related to systemic sclerosis [11] and [12]. However, its potential in monitoring disease progression and especially its predictive value of clinical complications is still debated. Capillaroscopic abnormalities are susceptible to significant change during patient follow-up. Rossi et al. [13, present issue] discuss the usefulness of scoring capillaroscopic alterations, which, albeit time-consuming, should be systematically used in order to monitor microangiopathy.

With regard to the workshop on high risk patients with antiphospholipid syndrome, in order to better define the clinical setting of thrombotic recurrences in thrombotic patients with APS, a systematic review of the literature as of 1999, including 8 cohort studies and 6 intervention studies, was carried out by Bazzan et al. [14, present issue]. Thrombotic recurrences, bleeding events, therapeutic strategies, antiphospholipid (aPL) profile, and possible inherited or acquired risk factors were evaluated. Emerging risk factors for thrombotic recurrences included the aPL “profile” (i.e., triple positivity: positive lupus anticoagulant, anticardiolipin and anti  $\beta$ 2-glycoprotein I antibodies), discontinuation of oral anticoagulant therapy (OAT), and associated general risk factors and inherited thrombophilia. APS vascular patients with high risk aPL profiles were found to have a high recurrence rate in spite of correct OAT treatment [15]. Aspirin did not significantly affect the incidence of thrombotic events in these APS patients. Pengo et al. [16, present issue] emphasize that the triple positivity identifies a highly pathogenic autoantibody (an anti domain I of  $\beta$ 2-glycoprotein I, which was proven to retain lupus anticoagulant activity). Patients and carriers with this profile carry a much higher risk of thrombosis and miscarriage than APS patients with positivity for only one test. Thus, very different risk categories exist among patients with APS as well as among carriers of aPL. Clinical studies and interventional trials should first take these high risk subjects into consideration [17].

Several sessions of the Turin Meeting were dedicated to the changing therapeutic strategies of immune-mediated diseases in the era of biologic drugs, and the staggering financial consequences of the expanding indications of these innovative approaches.

Treatments that were available prior to the advent of biological drugs could not control joint destruction and progression of disability in patients with rheumatoid arthritis (RA). Randomized clinical trials have shown that the five currently available TNF blockers improve the signs and symptoms of both early RA and long-standing RA and other inflammatory arthritides, that they prevent radiographic progression, and improve the patients' health-related quality of life. Although biologic drugs dramatically improve the quality of life of RA patients, they multiply direct medical costs. Indeed, annual treatment costs for RA patients rose from 4000 to 12,000 Euro over a five-year period (from 2000 to 2005). However, this estimate referred to direct costs alone. Modena et al. [18, present issue] analyzed the costs related to RA [19] and [20] considering both direct (pharmacological, surgical and rehabilitative) and indirect costs (including loss of work productivity), and, intangible costs (cost of suffering due to the deterioration of the quality of life of both patients and their families). The main factors affecting the best cost-effectiveness in the management of RA in clinical practice included the speed of action of the drug, the safety profile of the various drugs, and “tight control” in patient management. “Tight control” has been defined as a treatment strategy tailored to the individual RA patient, aimed at achieving a predefined level of low disease activity or remission within a defined period of time [21]. In order to pursue this goal, Epis et al. [22, present issue] emphasize the need for continuous monitoring of disease activity with early therapeutic adjustments, or switching to other therapeutic options.

Leardini et al. [23, present issue] carried out a detailed head to head comparison of different biological therapies for RA. They analyzed not only the costs of purchasing and administering the drug, but also those related to acute and chronic complications of therapy, especially infections [24]. Notably, contrary to widespread opinion concerning the higher cost of intravenous therapies as compared to other routes of administration due to the use of hospital facilities, the authors highlighted a 7.3% difference in favor of intravenous versus subcutaneous biologics. Leardini et al. also emphasized the difference between ex-factory prices, which are usually considered in pharmacoeconomic studies, and actual costs, which are about one third lower, arguing the superiority of innovative therapies in the management of RA.

With regard to the other immune-mediated diseases that biologic drugs are now being indicated for, glomerulonephritis (GN) accounts for 10%–20% of the total incident cases of end stage renal disease (ESRD), and is the third most common cause of ESRD after diabetes and hypertension in western countries. Research into the underlying mechanisms of several immune-mediated glomerular diseases has revealed the importance of auto-antibodies in these disease processes. In the last forty years, empirical treatment has been based upon the use of corticosteroids and/or immunosuppressive drugs. Pani analyzed [25, present issue] the risk-to-benefit balance of steroids and conventional immunosuppressive regimens focusing on idiopathic nephrotic syndrome (INS) and ANCA associated vasculitis [26], [27], [28] and [29]. Almost 95% of children affected by minimal change disease achieve remission of proteinuria within 4 to 8 weeks of prednisone administration. In adults with focal segmental glomerulosclerosis, prednisone induces at least partial remission in the majority of patients. More than 65% of patients with idiopathic membranous nephropathy reach complete or partial remission with a 6-month course of therapy alternating glucocorticoids with alkylating agents. Glucocorticoids plus cyclophosphamide, and, on occasion, plasmapheresis are effective in 70%–90% percent of patients with ANCA-associated vasculitis. However, although very effective, especially in the acute phase, corticosteroids, nucleotide synthesis inhibitors, alkylating agents and calcineurin inhibitors have severe side-effects. Therefore, we need drugs with more targeted mechanisms of action and fewer side effects in order to overcome the current limits of conventional immunosuppression [30]. Given the understanding that in several renal diseases, such as ANCA-associated vasculitis, mixed cryoglobulinemia, membranous nephropathy and lupus nephritis,

auto-antibodies have been implicated either in direct glomerular injury or as correlates with disease activity, rituximab has emerged as a potent option for many immune-mediated glomerulopathies. Based on recent large clinical trials, it has been FDA-approved for the treatment of ANCA-associated vasculitis and continues to be studied in off-label usage for many glomerular diseases, including membranous nephropathy, lupus nephritis, and mixed cryoglobulinemia [31], [32], [33], [34], [35], [36], [37], [38], [39], [40] and [41]. It has been used as a treatment in nephrotic syndrome in children and adults, including both minimal change disease and focal segmental glomerulosclerosis. Kattah et al. [42, present issue] discuss the current state of anti-CD20 therapy in several glomerular disease processes, and show that, given its efficacy, tolerability and safety profile as compared to conventional immunosuppressive regimens, RTX is rapidly emerging as an alternative treatment strategy in glomerular diseases.

As stated before for RA, major concerns are represented by the financial impact of these new therapeutic approaches, but apart from costs, the question is “should biological therapy be continued indefinitely”? Leardini et al. [23, present issue] just touched on this issue by examining the general safety of biologics. In our mind the impact of the possible adverse effects of conventional and novel drugs should be analyzed in the long term similar to the epidemiologic approach to second tumors occurring several decades after the chemotherapy of childhood cancer. In this context, a new concept of biologic therapy is emerging, at least for immune diseases that (although chronic in the clinical course) are mainly characterized by time-limited acute flares, i.e., short-intensive courses of combined conventional and biological therapy without maintenance immunosuppressive treatment [43] and [44]. This could limit both the costs and the sequelae of prolonged immunosuppression.

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